

REMARKS/ARGUMENTS

Applicants respectfully request reconsideration and allowance of this application in view of the amendments above and the following comments.

Claims 1, 3, 5, 12 and 15 were rejected under 35 USC § 103(a) as being obvious over Pillai et al. ("Pillai"), *Cancer Epidemiol. Biomarkers and Prevent.*, 5: 329-335 (1996), in view of Geiger et al. ("Geiger"), US 2002/0045591. In response, Applicants respectfully submit that the cited combination of references does not make out a *prima facie* case of obviousness. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

The instant claims are drawn to methods of detecting tumor cells and their precursor cells in uterine cervical smears, and positively specify in the last step of each the successful detection of tumor cells and their precursor cells in the uterine cervical smear. This is quite an advance as it is described in the instant specification that often detection of a single marker does not give a reliable indication of the presence of tumor cells because many such markers are present both in healthy cells and tumor cells. See numbered paragraph [0005] of US 2002/0106685. Further, at least two of the markers mentioned in Pillai fall into this category, viz., p53 and bcl-2. See the very end of numbered paragraph [0016] of US 2002/0106685. Accordingly, detection of these particular markers mentioned by Pillai would have been expected by persons skilled in the art not to be reliable indicators of the presence of tumor cells or their precursor cells in a uterine cervical smear.

According to the Examiner, persons skilled in the art, given Geiger's teachings related to triple immunofluorescence microscopy, would have been motivated to simultaneously detect

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Pillai's markers using colored reagents in order to save time, labor and reagents. Applicants respectfully disagree. Geiger's teachings are not clearly applicable to Pillai and, therefore, Applicants respectfully submit that persons skilled in the art would not have combined their teachings in such a way to achieve the present invention. Specifically, if such persons combined Pillai with Geiger's method, such combined method would still not have the color signal intensities combining and accrediting as required by the instant claims.

More importantly, such persons would not have expected that such combined Pillai + Geiger method, even if carried out, would reliably indicate the presence of tumor cells and their precursors in the uterine cervical smears. As noted above, two of Pillai's three markers, p53 and bcl-2, are markers that are known to persons skilled in the art *not* to give reliable indications by themselves of the presence in tested uterine cervical smears of tumor cells or their precursors. There is nothing in Pillai or in Geiger or in their combination that would have suggested to persons skilled in the art that detecting these two unreliable markers in combination should give a reliable indication of the presence of tumor cells or their precursors in the uterine cervical smears. However, as discussed in the instant specification and demonstrated in the instant examples, detecting two of these unreliable markers in a single cell under the conditions indicated provides a reliable indication whether or not the cell is a tumor cell or a precursor.

Since there is nothing in the combination of Pillai and Geiger to lead persons skilled in the art in this direction, Applicants respectfully submit that the rejected claims are not, in fact, *prima facie* obvious over the combination of Pillai and Geiger. Further, even if the rejected claims could be considered to be *prima facie* obvious over such combination, this is rebutted by the results reported in the instant specification about the reliability of the instant method. That

benefit of the present invention is nowhere taught nor suggested by the combination of Pillai and Geiger.

In view of the foregoing, Applicants respectfully submit that the Examiner would be fully justified to reconsider and withdraw this rejection. An early notice that this rejection has been reconsidered and withdrawn is earnestly solicited.

Applicants point out that new claims 16 and 17 have been added. New claim 16 depends on claim 1 and new claim 17 depends on claim 15. Both new claims provide that the marker "alone is not a reliable indicator of the presence of tumor cells or their precursor cells in said uterine cervical smear." This language is supported by numbered paragraph [0015] of US 2002/0106685. Both new claims also provide that "the combined and accredited signal intensities [are compared] to a threshold value, wherein combined and accredited signal intensities above or below the threshold value reliably indicate the presence of tumor cells and/or their precursors in thereby detecting tumor cells and their precursor cells in the uterine cervical smear." This language is supported by, for example, numbered paragraph [0017] of US 2002/0106685. Applicants do not believe that either claim 16 or 17 introduces new matter. An early notice to that effect is earnestly solicited.

Claims 1, 4 and 13 were rejected under 35 USC § 103(a) as being obvious over Pillai in view of Geiger and further in view of Kihana et al. ("Kihana"), *Cancer*, 73: 148-153 (1994).

Claim 14 was rejected under 35 USC § 103(a) as being obvious over Pillai in view of Geiger and further in view of Giuliano et al. ("Giuliano"), US 6,756,207.

In response to both of the immediately preceding obviousness rejections, Applicants submit that these were dependent upon the combination of Pillai and Geiger rendering prima

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facie obvious the basic features of the present invention, which Applicants have shown above is not the case. The secondary references Kihana and Giuliano do not bridge the gap between the instant claims and the combination of Pillai and Geiger. Consequently, the combinations of Pillai and Geiger and Kihana or Giuliano still fails to make out a prima facie case of obviousness. Therefore, Applicants respectfully request that the Examiner consider and withdraw this rejection as well.

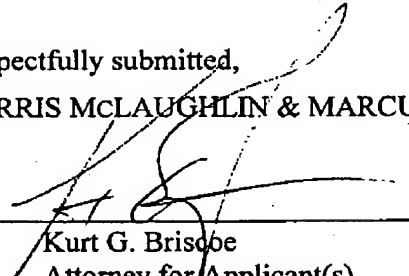
Applicants believe that the foregoing constitutes a bona fide response to all outstanding objections and rejections.

Applicants also believe that this application is in condition for immediate allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

Early and favorable action is earnestly solicited.

Respectfully submitted,
NORRIS MCLAUGHLIN & MARCUS, P.A.

By


Kurt G. Briscoe
Attorney for Applicant(s)
Reg. No. 33,141
875 Third Avenue
18th Floor
New York, New York 10022
Phone: (212) 808-0700
Fax: (212) 808-0844

CONDITIONAL PETITION FOR EXTENSION OF TIME

If entry and consideration of the amendments above requires an extension of time, Applicants respectfully request that this be considered a petition therefor. The Commissioner is authorized to charge any fee(s) due in this connection to Deposit Account No. 14-1263.

ADDITIONAL FEE

Please charge any insufficiency of fees, or credit any excess, to Deposit Account No. 14-1263.

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